REMARKS

In response to the Office Action of June 12, 2007, claims 66, 68-70 and 72 have been amended and new claims 73-89 have been added to more clearly define the claimed invention. Support for claims 76-78 and 82-84 can be found in Examples 30 and 39 (pages 69-70 and 76, respectively), which demonstrate the nucleic acid ligands of the instant invention are functional antagonists of P-selectin. Support for new claim 88 can be found in Examples 33 and 38 (pages 71 and 75), which demonstrate that the nucleic acid ligands of the instant invention specifically bind to P-selectin expressed on the surface of the platelet cell. Support for new claim 89 can be found in Examples 30 and 39, which demonstrate that the nucleic acid ligands of the instant invention inhibit the binding of P-selectin to the carbohydrate sialyl-Lewis^x, together with the Summary of the Invention which provides: "Further included in this invention are nucleic acid ligands to lectins that have substantially the same structural form as the ligands presented herein and that have substantially the same ability to bind lectins and antagonize the ability of the lectin to bind carbohydrates." (page 10, lines 23-27, emphasis added). Support for new claims 73, 79, and 85 can be found in Table 19, which illustrates that the fragment identified as SEQ ID NO: 223 is an active truncate of SEQ ID NO: 206, identified by the boundary experiments described in Example 27 (page 65). Finally, support for new claims 74-75, 80-81 and 86-87 can be found in Examples 27 and 34 (pages 65-66 and 72), which describe the post-SELEX synthesis, 2'-OMe modified nucleic acid ligands. As described in Example 34 "up to 15 positions may be substituted with only slight losses in affinity." Applicant is aware of the sequence listing requirements and will submit a sequence listing which includes SEQ ID NO: 391 in due course. As detailed below, Applicant asserts that the claims, as amended, are fully supported and enabled by the Specification.

Claims 65, 66, 68-70 and 72 were rejected under 35 U.S.C. § 112, first paragraph and under the judicially created doctrine of obviousness-type double patenting. Claims 66, 68, 70 and 72 were rejected under 35 U.S.C. § 112, second paragraph. Each of the rejections is addressed below.

Rejection Under 35 U.S.C. § 112, First Paragraph

The Examiner has maintained the rejection of claims 65, 66, 68-70 and 72 under 35 U.S.C. § 112, first paragraph as failing to comply with the enablement requirement. The first

paragraph of Section 112 requires that a patent application be written so as to "enable any person skilled in the art to which it pertains . . . to make and use the same." A specification is presumed to be enabling absent "a reason to doubt the objective truth of the statements contained therein." *In re Marzocchi*, 169 U.S.P.Q. 367, 369 (C.C.P.A 1971).

The instant invention is drawn to methods for treating lectin-mediated platelet disorders (independent claims 65, 76, 82, 88 and 89) and methods for treating lectin-mediated inflammation or lymphocyte trafficking disorders (independent claim 69). The methods comprise administering to a mammal a nucleic acid to P-selectin and L-selectin, respectively . The Examiner asserts that one of ordinary skill in the art would not have known how to use the nucleic acid ligands as therapeutics, nor determine whether the ligand would function as a pharmaceutical agent to treat a particular disorder without appropriate "*in vivo* evidence". In making this rejection the Examiner emphasizes that the administration of nucleic acids to patients for treatment or therapy is a difficult and unpredictable field. In response, Applicant submits that the illustrative examples provided in the specification teach a method of making and using a nucleic acid ligand to a lectin, to inhibit lectins, to mediate lectin-dependent processes, and therefore to treat lectin-mediated disorders. As such, Applicant respectfully traverses this rejection.

As detailed in the Amendments and Remarks document filed on May 23, 2007, a number of working examples provide the necessary guidance for the steps necessary in order to recognize or identify any inhibition of lectin activity by a nucleic acid ligand in conditions or diseases mediated by lectins, including P-selectin and L-selectin. It has been determined by the courts that no working examples are required to enable a patent application. *In re Borkowski*, 422 F.2d 904, 164 U.S.P.Q. 642 (C.C.P.A. 1970) (see also MPEP § 2164.02, page 2100-196, col. 1, which provides that "[c]ompliance with the enablement requirement . . . does not turn on whether an example is disclosed. . . . An applicant need not have actually reduced the invention to practice prior to filing"). In the instant case, however, Applicant provides *in vivo* Examples, which indicate the specificity and efficacy of the ligands in the claimed methods in accepted model systems. Regarding the correlation between *in vitro* and *in vivo* data the MPEP provides:

> Since the initial burden is on the examiner to give reasons for the lack of enablement, the examiner must also give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model example. A rigorous or an

> invariable exact correlation between an *in vivo* or *in vitro* model and the claimed method is not required, rather, only a reasonable correlation is required.

(MPEP, § 2164.02, page 2100-196, col.2, citing *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985)). As such, a specification "may be enabling even though some experimentation is necessary," *United States v. Teletronics, Inc.*, 857 F.2d 778, 8 U.S.P.Q.2d 1217, 1223 (Fed. Cir. 1988), so long as the amount of experimentation required is not "undue experimentation." *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). The test is whether the specification "provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Id.*, 858 F.2d at 737, 8 U.S.P.Q.2d at 1404. The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *Id.*, 858 F.2d at 737, 8 U.S.P.Q.2d at 1404.

Much guidance and direction exists in the prior art with regard to details of treatment regimens for antisense and other nucleic acid therapeutics, which have been used in the treatment of humans since at least as early as 1993. The Examiner cites Stull and Szoka (1995) *Pharmaceutical Research* 12(4):465, 477-478, as teaching that "the delivery and entry of nucleic acid drugs into the target site remains a major obstacle to the successful introduction of this aspect of the molecular biology evolution into a clinical setting." However, the asserted problems in the prior art highlighted by the Examiner relate to the admittedly much more difficult intracellular delivery of these compounds, rather than the extracellular delivery as in the instant case. See e.g., Stull and Szoka (page 476, col. 2) which provides in relevant part:

> It is clear, however, that application of these expensive compounds *in vivo* requires many problems be solved, some of which have been discussed above in conjunction with studies performed in cell culture, but particularly those related to delivery *in vivo* of nucleic acids to the cytoplasm of specific cells.

(emphasis added). Applicant maintains therefore that the art relied upon by the Examiner as teaching the difficulty and unpredictability of administering nucleic acid drugs is not relevant to the claims of the instant application.

While development of a specific treatment regimen may require a large quantity of experimentation, the amount of experimentation is not a controlling factor. It is a tenet of patent law that an applicant need not teach what the skilled artisan already knows. Instead, it is preferred that an applicant "omit what is known in the art." *Hybritech Inc. v. Monoclonal Antibodies*, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986). Certainly, much guidance and direction exists

in the prior art with regard to administration routes and other details of treatment regimens. Additionally, as noted in the Amendments and Remarks document filed on May 23, 2007, the specification provides extensive teaching on the preparation, administration, and analysis of treatment data in *in vivo* experiments. Applicants submit that such prior art treatments, together with the specification, provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed and, and therefore satisfy the enablement requirement with respect to the administration of compounds of the claimed methods. While some experimentation is necessary to develop specific experimental protocols, such experimentation is not undue, but rather routine for the reasons explained.

The specification explains that it is expected in the art that antagonists to lectins that recognize exogenous carbohydrates may have wide application for the prevention of infectious diseases at page 3, line 35 to page 4, line 35, for example. Furthermore, the specification also references animal models available for testing the efficacy of oligonucleotide antagonists to lectins at page 19, line 34, to page 20, line 35.

Specifically, working examples 7-11 describe the generation of high-affinity 2'-NH_2 ligands to human L-selectin. The ligands generated have affinities that are several orders of magnitude higher than that of natural carbohydrate ligands. Furthermore, the ligands bind to L-selectin on a cell surface in a saturable fashion, and are capable of inhibiting L-selectin binding to sialyl-Lewis^x. Working examples 22-25 describe a similar set of experiments and similar results for 2'-F RNA ligands to L-selectin.

Working examples 13-20 describe a similar set of experiments and similar results for ssDNA ligands to L-selectin. Furthermore, experiments on lymphocyte trafficking, an L-selectin dependent process, are described (Examples 13H and 20). Lymphocyte trafficking to peripheral lymph nodes is exquisitely dependent on L-selectin. The tested L-selectin ligand was able to block lymphocyte trafficking in this *in vivo* system.

Examples 27-34 similarly describe the generation and *in vitro* and *in vivo* properties of 2'-F RNA ligands to P-selectin. The ligands bind to human platelets in a P-selectin specific manner. Examples 36-39 describe the generation and properties of 2'-NH_2 nucleic acid ligands to human P-selectin.

As indicated above, the specification provides a number of references to accepted model systems in which to evaluate the efficacy of oligonucleotide selectin antagonists at page 19, line

34 to page 20, line 35. Thus, the prior art provides evidence of a correlation between model systems and treatment. In addition, the subsequent literature has reported the successful use of the currently claimed methods. Enclosed is a copy of Jenison *et al.* (Aug. 1998) "Oligonucleotide Inhibitors of P-Selectin-Dependent Neutrophil-Platelet Adhesion" *Antisense Nucleic Acid Drug Dev.* 8(4):265-279. One of the authors of this article, David Parma, is also a named inventor in the instant application. This article is being submitted to show that the present invention was enabled at the time of filing. Jenison *et al.* report that *in vitro*, aptamers bind with subnanomolar affinities to P-selectin expressed on thrombin-activated platelets, inhibit the binding of P-selectin-IgG chimera to sLe^X and to neutrophils, and block the binding activated platelets to neutrophils in flow cytometry and in hydrodynamic assays. Extrapolating from their *in vitro* characteristics, the article reports that novel P-selectin-specific antagonists are suitable candidates for therapeutic development.

Also enclosed herewith is a copy of Watson *et al.* (April 2000) "Anti-L-Selectin Aptamers: Binding Characteristics, Pharmacokinetic Parameters, and Activity Against an Intravascular Target *In Vivo*," *Antisense Nucleic Acid Drug Dev.* 10(2):63-75. David Parma is also one of the authors of this article. This article reports binding characteristics *in vitro*, pharmacokinetic parameters in Sprague-Dawley rats, and inhibitory activity in a SCID mouse/human lymphocyte model of lymphocyte trafficking for both 2'F pyrimidine 2'OH purine RNA and ssDNA anti-human L-selectin aptamers. The data indicate that aptamers with low nanomolar affinity are suitable candidates for use as *in vivo* reagents and that nonspecific binding to vascular cells is not an issue for efficacy. The article reports that pharmacokinetic parameters and *in vivo* activity are significantly improved by conjugating aptamers to a carrier molecule, such as polyethylene glycol (PEG). Most active *in vivo* is 1d40, a 2'F pyrimidine 2'OH purine aptamer conjugated to 40 kDa PEG. At a dose of 5.4 nmol/kg body weight, its duration of effect (time to 50% inhibition) is 11.2 hours, and at 1 mg or 90 nmol/kg, its plasma clearance rate (CL) is 0.4 ml/min/kg. Its ED50 is estimated to be 80 pmol/kg in preinjection dose-response experiments, compared with 4 pmol/kg for the dimeric anti-L-selectin antibody DREG56. The data indicate that properly formulated aptamers have the capacity to be effective therapeutic agents against intravascular lectin targets.

In summary, Applicant maintains that the method of treatment claims of the instant invention are enabled by the amount of direction and guidance in the specification, coupled with

the knowledge available in the prior art, and the presence of working examples showing *in vitro* and *in vivo* data with a reasonable correlation to the claimed treatment methods. Furthermore, the subsequent literature is further evidence that the invention is enabled. Reconsideration is respectfully requested.

Obviousness-type Double Patenting

The Examiner has rejected claims 65, 66, 68-70 and 72 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 6 and 7 of U.S. Patent No. 6,544,959. Appropriate action will be taken when necessary to ensure there will be no double patenting.

Rejections under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 66, 68, 70 and 72 under 35 U.S.C. § 112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Specifically the Examiner maintains that there is insufficient antecedent basis for the phrase "said nucleic acid ligand to a lectin" in lines 1-2 of claims 66, 68, 70 and 72. In response, claims 66 and 68 have been amended to read "said nucleic acid ligand to P-selectin" and claims 70 and 72 have been amended to read "said nucleic acid ligand to L-selectin." Claim 69 has also been amended to correct a typographical error.

Applicant believes that the pending claims are now in condition for allowance. If it would be helpful to obtain favorable consideration of this case, the Examiner is encouraged to call and discuss this case with the undersigned.

This constitutes a request for any needed extension of time and an authorization to charge all fees therefore to deposit account No. 19-5117 if not otherwise specifically requested. The undersigned hereby authorizes the charge of any fees created by the filing of this document or any deficiency of fees submitted herewith to be charged to deposit account No. 19-5117.

Respectfully submitted,

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